Educational attainment of children born to mothers with epilepsy

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Abstract

Objective

Small prospective studies have identified that children exposed to valproate *in utero* have poorer scores on cognitive testing. We wanted to identify whether children exposed to antiepileptic drugs (AEDs) in utero have poorer school performance.

Methods

We used anonymized, linked, routinely-collected healthcare records to identify children born to mothers with epilepsy. We linked these children to their national attainment Key-Stage 1 (KS1) tests in mathematics, language and science at the age of seven and compared them to matched-children born to mothers without epilepsy, and to the national KS1 results. We used the core subject indicator (CSI) as an outcome measure (the proportion of children achieving a minimum standard in all subjects) and the results in individual subjects.

Results

We identified 440 children born to mothers with epilepsy with available KS1 results. Compared to a matched control group, fewer children with mothers being prescribed sodium valproate during pregnancy achieved the national minimum standard in core subject indicator by (-12.7% less than the control group), mathematics (-12.1%), language (-10.4%) and in science (-12.2%). Even fewer children with mothers being prescribed multiple AEDs during pregnancy achieved a national minimum standard: core subject indicator by (-20.7% less than the control group), mathematics (-21.9%), language (-19.3%), and science (-19.4%). We did not observe any significant difference in children whose mothers were prescribed carbamazepine or were not taking an AED when compared to the control group.

Conclusions

In utero exposure to AEDs in combination, or sodium valproate alone, are associated with a significant decrease in attainment in national educational tests for seven-year-old children compared to both a matched control group and the all-Wales national average. These results give further support to the cognitive and developmental effects of *in utero* exposure to sodium valproate as well as multiple AEDs, which should be balanced against the need for effective seizure control for women during pregnancy.

Key words: Epilepsy, Educational attainment, Antiepileptic drugs, Case-control study, Clinical decision support

Introduction

Valproate is the most effective drug for treating genetic generalized epilepsy,[1] but recent prospective psychometric studies have demonstrated cognitive impairment and neurodevelopmental disorders in 30–40% of children exposed to valproate *in utero,*[2,3] as well as a significant decrease in intelligence quotient(IQ).[4,5] Women with epilepsy who have satisfactory control with valproate and are planning a family therefore have a difficult decision to make.

In the United Kingdom the Medicines and Healthcare Products Regulatory Agency (MHRA), issued stringent guidance for all clinicians prescribing valproate to women of child-bearing potential in 2015. This guidance was updated in 2017 based on evidence that women are still not aware of the risks of taking valproate during pregnancy.[6] An International League Against Epilepsy (ILAE) task force made seven recommendations, the first of which is "*Where possible*, valproate should be avoided in women of childbearing potential." Women with epilepsy who are taking AEDs are presently advised to continue them throughout pregnancy, primarily because of the risks of convulsive seizures to the mother and her unborn child.

To be able to counsel mothers adequately about the risks of uncontrolled seizures during pregnancy and cognitive outcomes for their children, it is important to know whether the psychometric differences demonstrated in research conditions translate to children in the community. We aim to investigate the effect of AED exposure *in utero* on the educational attainment of children born to mothers with epilepsy using anonymized, routinely-collected healthcare records and the results of a standard national educational assessment.

Methods

Cohort Selection

We used the Secure Anonymous Information Linkage databank (SAIL)[7,8] to access routinely-collected healthcare records and identify women who had been diagnosed with epilepsy before becoming pregnant. All studies using SAIL data need independent Information Governance Review Panel (IGRP) approval. This study obtained IGRP approval ref 0228. The Research Ethics Service has previously confirmed that SAIL projects using anonymised routinely collected data do not need require specific NHS research ethics committee approval.

In Wales, every individual is assigned a National Health Service general practitioner (GP). SAIL currently contains primary care records for 80% of Welsh GPs corresponding to 77% of the Welsh population (approximately 2.3 million people). GPs provide primary health care, prescribe medication, and maintain health records for individuals. GPs will prescribe AEDs for people with epilepsy in almost all cases, but the current standard of care is that everyone with a suspected seizure is first seen by a 'specialist' (neurologist or epileptologist) within two weeks of their first event. [9-10] Medication is first prescribed by the specialist at or following this visit. A letter with details of the diagnosis and AED prescription is subsequently sent to the patient's GP.

We defined a person as having a diagnosis of epilepsy if their GP record contained an epilepsy diagnosis code as well as a record of repeat AED prescriptions. [11–14] Currently seizure type, seizure frequency, and AED daily doses are not accurately available from the datasets held within SAIL.

Educational assessment in England and Wales

Between 1999 and 2011, children in Wales were assessed over five Key Stages (KS) between 7 and 16 years of age. These tests were a national measure of educational achievement children in Wales and therefore provide a standardized measure of educational attainment. Every child is tested in mathematics, language (English or Welsh) and science and is awarded a level between 1 (lowest) and 3 (highest). In certain circumstances children may obtain an unclassified or "working towards" meaning that they do not achieve the required grade to pass the year. KS1 assessment takes place at

the age of 7 years. The core subject indicator (CSI) is defined as the proportion of children achieving a minimum standard in all three KS1 subjects, that being a level 2 or higher in each subject.

In 2011, in Wales, the KS1 system for 5–7 year olds was combined with the Early Years assessment for children between 3–5 years of age and is now called the Foundation Phase to assess children between the ages of 3–7 years of age. Key Stage 1 for 5–7 year olds was not combined with earlier years in England, and is still used as a standard test. We were able to obtain a subset of results from the Welsh Government in the pre-2011 phase to assess the educational achievement of children in KS1 born to mothers with epilepsy. For these children, we linked data from the Department for Children, Education, Lifelong Learning and Skills (DCELLS) dataset and their corresponding 2003–2008 KS1 results to their birth records and their mothers' GP records in the SAIL Databank.[15]

Education Data Ascertainment

Given that KS1 results (taken at the age of 7) were only available within SAIL for the years 2003–2008 at the time of this study, we searched for women with epilepsy who gave birth between 1996 and 2001 and had children who had KS1 results which were accessible within SAIL. We divided the mothers into groups based on the AED that they were prescribed during pregnancy (including those that were not prescribed an AED) and created a control group (with 4:1 matching) matched for maternal age, week of gestational age, and deprivation at the time of birth. We used the Welsh Index of Multiple Deprivation (WIMD) as a measure of deprivation.[13] Information on any additional learning support that individual children may have had was not available.

Statistical Analyses

We used R version 3.2.0 to conduct the statistical analyses. We used a Chi-square significance test to compare the KS1 results of each group and performed a conservative Bonferroni correction using the "p.adjust ()" function that multiplies the raw p-value by the number of independent tests, and calculated confidence limits using the "summaryCE ()" function from the Rmisc package.

Results

Cohort profile

We identified 440 children with KS1 results available between 2003 and 2008 who had mothers with epilepsy diagnosed before their pregnancy and had GP records within SAIL. We defined five groups of mothers prescribed the following AEDs: monotherapy with carbamazepine, lamotrigine, or sodium valproate, multiple AEDs as well as no AED prescription (see Table 1). 20 of the 39 mothers (54%) in the polytherapy group were prescribed sodium valproate as one of their AEDs. Further details on the 15 different combinations of AEDs prescribed in the polytherapy group can be seen in Tables 2 and 3. The numbers for the polytherapy combinations are small, we therefore did not perform any analysis on these sub-groups, but present results for the polytherapy group as a whole. We did however analyse educational attainment in the polytherapy group when split into those on polytherapy treatment with sodium valproate and those on polytherapy treatment without sodium valproate, but we found no significant difference between these two groups across any attainment indicator (please see Table 4).

Reference data for the control variables (gestational age, maternal age and WIMD score) in each group are reported in table 1. There was no significant difference in the mean of these variables when compared to controls. We have included results for all children in Wales in table 1 to provide context to the KS1 results. Since we have prescription data only we are unable to comment on AED adherence, but we do not expect adherence to differ across different AED prescriptions. The proportion of children in each group achieving at least a level 2 in each subject is shown in Figure 1.

Figure 1 – *Key Stage 1 results stratified by subject and study groups. Each group was compared to the matched control group. Significant differences in attainment (* $p < 0.05$, ** $p < 0.005$) between each group and the matched control are shown. The p-values have been Bonferroni corrected for multiple testing (see Methods section). The All Wales group is shown as a regional comparator only and not used to test for significance.*

Children born to mothers with epilepsy being prescribed sodium valproate during pregnancy have a lower level of achievement in KS1 tests across all indicators other than language. Fewer children exposed to sodium valproate *in utero* achieve the minimum standard when compared to the matched control group by: CSI = -12.7% (p=0.035) less than the control group, mathematics = -12.1% (p=0.011), language = -10.4% (p=0.188) and science = -12.2% (p<=0.004) (p-values are Bonferroni corrected for multiple testing – see Methods section). Children born to mothers with epilepsy being prescribed multiple AEDs during pregnancy also have a lower level of achievement across all indicators other than language when compared to the matched control group by: CSI = -20.7% (p=0.042) less than the matched control group, mathematics = -21.9% (p=<0.007), language = -19.3%(p=0.269) and science = -19.4% (p=0.010) (p-values are Bonferroni corrected for multiple testing – see Methods section). We did not find a significant decrease in attainment in children born to mothers with epilepsy that were not prescribed an AED during pregnancy. Excluding children with epilepsy and mothers who were recorded as smoking during pregnancy did not change the results in terms of significant results.

Discussion

We demonstrate through the analysis of linked data in the SAIL databank that mothers being prescribed multiple AEDs and those being prescribed sodium valproate have children with significantly poorer attainment in national tests at the age of seven. In contrast there was no difference seen in children exposed to carbamazepine, lamotrigine or mothers that did not take drugs during pregnancy, however we note that the sample size for the lamotrigine group is small. Our findings support previous studies that provide consistent evidence that *in utero* exposure to sodium valproate and AEDs in combination are linked to adverse neurodevelopmental outcomes. Mothers not prescribed any drug during pregnancy do not appear to give birth to children that have decreased educational attainment as compared to the

control group. This might be expected given both groups are not exposed to AEDs. It is also possible that the mothers with epilepsy not taking AEDs have less frequent seizures, thus reducing the risks to the unborn child associated with exposure to maternal seizures.[16] We acknowledge factors such as parental intelligence quotient (IQ) and social and behavioral issues can also have an effect on educational outcome, and so must be taken into context with the results presented in this study.

The strength of this study is the ability to select a large cohort of 440 children with national test results without major recruitment bias and compare to a large control group. We created a control cohort matched on maternal age, gestational age and socioeconomic deprivation, but we were unable to control for maternal body weight at time of pregnancy. The children born to mothers with epilepsy in this study have an increased deprivation score when compared to Welsh children as a whole, as is expected given the association with epilepsy and deprivation. [14] Using a standardized national assessment as a measure of performance ensures that each child has the opportunity to be assessed based on the same curriculum, and as such these results would closer reflect the learning experience of children at this age compared to an IQ test.

The main limitation of this study is not being able to use maternal IQ, as well as other maternal factors such as maternal weight or alcohol consumption during pregnancy, as covariates. [4,5] Children born to mothers with epilepsy may have other conditions which affect their ability to perform in the KS1 tests and we have not specifically looked for these although we have recorded the number of children with epilepsy. We have been unable to account for parental style and/or ability in this study which may influence educational attainment. It is also possible that mothers with poorly controlled seizures may have an effect on their child's education in terms of parental support outside of school settings, but this information is difficult to ascertain and is not available to any comprehensive standard within the SAIL databank.

Another limitation of this study is that we are unable to report on AED dosage, although other studies have reported significant cognitive impairment even at low dosages of sodium valproate.

It is possible that the mothers prescribed sodium valproate as well as those prescribed multiple AEDs have more severe epilepsy and this may explain the difference in KS1 results. We are currently unable to measure seizure frequency / epilepsy severity, identify epilepsy type, or ascertain alcohol and illicit drug use accurately from SAIL data. Another factor that could have influenced educational attainment is the lack of preconception/perinatal folic acid prescription, which we were not available to ascertain accurately, as this is available without prescription and frequently taken 'over the counter'.

Although our cohort is large, we do not have sufficient outcomes to look at other AEDs, or to look at different AED combinations in detail. We were not able to report any results for drugs, such as levetiracetam, introduced after the window for pregnancy (1996–2001) that we used in this study. This time period was limited by the period that KS1 results were available within SAIL (2003–2008).

Our results support the evidence of many independent studies that have reported cognitive impairment of children exposed to sodium valproate *in utero*. The NEAD study found a 9-point decrease in IQ in children at three and six years old who were born to mothers taking sodium valproate during pregnancy[4,5] as well as decreased motor, emotional and behavioral/adaptive functioning in children at three years old.[17] Studies based on the UK Epilepsy and Pregnancy Register have found an association between sodium valproate and a decrease in cognitive development with early cognitive delay that suggests children are at a disadvantage well before school age.[18-19] While this study finds a statistically non-significant trend in language at KS1, other studies have shown decreased language and verbal skills at an early infant stage.[20-22]

Previous studies have found an association with carbamazepine exposure and cognitive impairment, there are other studies have found no association between carbamazepine exposure and cognitive impairment; our study supports the latter with no evidence of decreased educational attainment at school age.[23]

While this study highlights the risk of cognitive effects in the children of mothers prescribed sodium valproate or multiple AEDs, it is important to acknowledge that some epilepsies are difficult to treat without these treatment regimes. Despite this, our results add to the growing evidence that *in utero* exposure to certain AEDs can cause developmental problems in children. Women with epilepsy should be informed of this risk and alternative treatment regimens should be discussed before their pregnancy with a physician that specializes in epilepsy.

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Footnotes

Contributors Conceived and designed the study: AL, WP, RT, CW, MK, and MR. Performed the study: AL. Performed statistical analysis: AL. Wrote the paper: AL. Critical revision of the manuscript: AL, WP, RT, CW, MK, and MR.

Competing interests None declared.

Patient consent Not needed due to only using anonymised routinely collected patient data.

Ethics approval This study was approved by SAIL's independent Information Governance Review Panel (project 0228). The National Research Ethics Service has confirmed that SAIL projects using anonymised data do not require specific NHS research ethics committee approval.